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Gary L. Griffiths

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FAEGRE & BENSON LLP

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CANELLA, KAREN A

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/706,852	Applicant(s) GRIFFITHS ET AL.	
	Examiner Karen A. Canella	Art Unit 1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 1-21,23-55,57-89 and 91-125 is/are pending in the application.
- 4a) Of the above claim(s) 43-55,57-89,91-118 and 120-124 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☐ Claim(s) 1-21,23-41 and 125 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>11/30/2004</u> . | 6) <input type="checkbox"/> Other: ____ |

DETAILED ACTION

Claims 1, 4-18, 21, 35, 36, 38, 40, 41, 72, 86 have been amended. Claims 1-21, 23-55, 57-89 and 91-125 are pending. Claims 43-55, 57-89, 91-118, 120-124 remain withdrawn from consideration. Claims 1-21, 23-41 and 125 are under consideration.

Applicant argues that the prior filed applications provide an adequate written description of the invention as it relates to conjugation of the anti-CD74 antibody to nanoparticles. Applicant sets forth text of U.S. 6,306,393 regarding the conjugation of anti-CD22 and anti-CD19 antibodies to submicron lipid emulsions. This description fails to adequately describe the genus of conjugates now claimed which are anti-CD74-nanoparticle conjugates because disclosure of an anti-CD19 conjugate or anti-CD22 antibody conjugate is not commensurate with the disclosure of an anti-CD74 antibody conjugate, and because a submicron lipid emulsion, although fulfilling the limitation of a species of "nanoparticle", is much narrower in scope than a generic "nanoparticle". Accordingly, the instant application will be given the effective priority date commensurate with the disclosure of 60/478,830, June 17, 2003, which describes CD74 binding molecules conjugated to nanoparticles.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 38 and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 38 recites a fusion protein comprising the light and heavy chains of scFv or Fv. The metes and bounds of the claim is unclear because scFv and Fv have a single chain and therefore do not have separate light and heavy chains.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

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pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11, 12, 21, 32, 33, 39 and 41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for effectors which are drugs, toxins, radioisotopes or a photodynamic agent, and CD74 binding antibodies, does not reasonably provide enablement for antibodies which bind to CD74 which are multispecific and inclusion of further binding molecules which bind to antigens which are not known to be related to the B cell dyscrasias or hematopoietic cells expressing MHC II, such as CD4, CD5, CD8, CD40L (also known as gp39 and CD154) MUC1, MUC2, MUC3, MUC4, tenascin, VEGF, EGFR, CEA, placental growth factor, carbonic anhydrase IX, CSAp and IIGF, and effectors which are immunomodulators, enzymes, hormones, or antiangiogenic molecules listed in claim 34, CD74 binding multispecific molecules which target antigens which are not CD74 or diabodies, triabodies and tetrabodies which bind to CD74. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant claims are drawn in part to a composition comprising one or more anti-CD74 binding molecules conjugated to one of more lipids, polymeric carriers, micelles or nanoparticles and one or more effectors, further comprising binding molecules which specifically bind to T cells via CD4, CD5, CD8, the MUC antigens, tenascin, carbonic anhydrase IX, vascular endothelial growth factor receptor, epidermal growth factor receptor, carcinoembryonic antigen, CSAp, which is a colon-specific antigen peptide, and IIGf, which is insulin-like growth factor. The instant specification states that CD74 expressing diseases are "immune dysfunction diseases, autoimmune disease, graft vs host, organ graft disease, a solid tumor, non-Hodgkin's lymphoma, Hodgkin's lymphoma, multiple myeloma, , B cell malignancy, or a T cell malignancy and that solid tumors include melanomas, carcinomas, sarcomas and/or gliomas.

Claim 21 requires in part effector molecules which are enzymes, or hormones. The specification has not taught how to use a hormone in a composition which comprises a CD74 binding molecule which is targeted to the known cancer cell types which express the MHC II invariant receptor, such as B cell malignancies and Hodgkin's lymphoma or any other cancer cell

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which expresses the CD74 molecule and therefore one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to make and use the broadly claimed invention as it encompasses effectors which are “hormones”.

Claim 39 requires that the fusion protein of claim 39 is multivalent and multispecific. when given the broadest reasonable interpretation, the term “multispecific” includes binding molecules which target antigens other than CD74. Claim 41 requires a diabody, triabody or tetrabody. Hannsen et al (Biochemical Journal, 1996, Vol 320, pp. 293-300) teach that the invariant chain of MHC II is rapidly internalized and that antibodies binding thereto are catabolized (page 298, second column, lines 1-7). Hannsen et al teach that this rapid uptake can be used to deliver toxins, radioisotopes, drugs that can kill tumor cells expressing Ii, such as B-cell lymphoma (page 299, second column, lines 1-5 of the last paragraph). The specification fails to teach a use for a CD74 binding molecule which is multispecific because of the rapid uptake of the CD74 receptor.. One of skill in the art would reasonable conclude that if a multispecific binding protein which includes CD74 binding were administered to a patient having a cancer expressing CD74, the rapid internalization of the bi-specific or multispecific antibody after binding to CD74 would prevent the binding of the non-CD74 specificities to their respective targets and thus prevent the specific therapeutic effect intended.

Claim 21 requires and effector which is an immunomodulator. Claim 32 is drawn to the composition of claim 1 comprising an immunomodulator. Claim 33 requires an immunomodulator which comprises various interleukins, interferons, G and GM colony stimulating factors. The art recognizes that interleukins such as Il6 and Il-10 contributed to the developments and pathogenicity of B cell lymphomas (abstract of Breen et al, Clinical Immunology, 2003, vol. 109, pp. 119-129 and the abstract of Nagel et al, Leukemia, 2005, vol. 19, pp. 841-846). The specification has not provided guidance on how to use the requires interleukins and cytokines to treat B cell lymphomas which could potentially stimulate and/or increase the malignant cells. Further regarding the teachings of Hannsen et al above, one of skill in the art would expect that the immunomodulators and interleukins conjugated to the anti-CD74 antibody would be internalized. The specification has not provided any objective evidence that an immunomodulator or interleukin delivered to the cytosol by an internalized anti-CD74 antibody would exert a therapeutic effect. therefore one of skill in the art would be subject to

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undue experimentation without reasonable expectation of success in order to use the instant compositions requiring immunomodulators, cytokines and interleukins.

Applicant argues that the art provides the enablement for the use of “hormones” as cytotoxic agents and cites U.S. 5,697,902, 5,716,595, 5,482,698 and 5,851,527. This has been considered but not found persuasive. The invention of U.S. 5,697,902 pertains to the targeting of hormone receptors, not the broadly claimed use of “hormones” as cytotoxic agents. The inventions of U.S. 5,716,595 and 5,482,698 are drawn to the detection of lesions using radio labeled hormones and biotin-conjugated hormones, respectively to bind to lesions having hormone receptors, which differs from the instant claimed inventions using “hormones” as cytotoxic agents. The inventions of 5,482,698 uses cytotoxic agents which are boron addends, drugs, toxins, radioisotopes, vasodilators, cytokine, radio sensitizers or photosensitizers and makes no mention of “hormones”

Applicants arguments that bi-specific antibodies are well known in the art do not address the specific concerns above, regarding the internalization of the CD74 target and the relative rate of internalization versus reaction with the non-CD74 specificity of the bi-specific or multispecific antibodies. Thus it is not a question of how to “make” said multispecific antibodies but how to use said antibodies having multiple binding targets when one of the specificities is targeted toward the rapidly internalized CD74.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

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the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-10, 13-21, 27, 35, and 125 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pawlak-Byczkowska et al (Cancer Research, 1989, Vol. 49, pp. 4568-4577) as evidenced by Juweid et al (Nuclear Medicine Communications, 1997, Vol. 18, pp. 142-148) in view of Lundberg et al (Journal of Pharmacy and Pharmacology, 1999, Vol. 51, pp. 1099-1105) and Hansen et al (Biochemical Journal, 1996, Vol. 320, pp. 293-300)..

Pawlak-Byczkowska et al teach that the EPB-1 monoclonal antibody, which is identified by Juweid et al to be the LL1 antibody (Juweid, *ibid*, page 142, second column, last two lines). Pawlak-Byczkowska et al teach that the EPB-1 antibody discriminated between lymphoid and non-lymphoid tissue and did not cross react with solid tumor tissue specimens (abstract). Pawlak-Byczkowska et al suggest that the antibody is an appropriate candidate for radioimmunodetection and radioimmunotherapy of B cell neoplasms (page 4568, second column, lines 5-10). Pawlak-Byczkowska et al do not teach the specific composition comprising a LL1 conjugate and one or more effectors.

Lundberg et al teach conjugation of the LL2 antibody (which is the Pawlak-Byczkowska EPB-2 antibody, Lundberg, *ibid*, page 1099, first column, lines 8-10) with a long-circulating drug carrier lipid emulsion. Lundberg et al teach that submicron lipid emulsions have hydrophobic cores which can solubilize considerable amounts of lipophilic drugs (page 1099, second column, lines 12-14), which fulfills the specific embodiment of claim 7 requiring a nanoparticle.. Lundberg et al teach that because LL2 is internalized into cells it facilitated intracellular delivery of cytotoxic agents (page 1099, column 1-2, bridging sentence). Lundberg et al teach that the problem of rapid uptake by mononuclear phagocytes is overcome by engrafting polyethylene chains on the particle surfaces with the monoclonal antibody linked to the distal PEG terminus (page 1100, first column, lines 1-9). Lundberg et al teach the conjugation of the antibody to a lipid by a sulfide linkage to PEG (Figure 1). Lundberg et al teach the lipids of DPPc and DPPe which fulfill the embodiment of claim 13 requiring amphiphilicity. Lundberg et al teach the reaction of DSPE with the distal terminus of the PEG

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chain thus fulfilling the specific limitation of claim 14 requiring a nucleophilic carbon (page 1100, first column, last seven lines). Lundberg et al teach a maleimide group at a distal terminus (Figure 1, top structure) thus fulfilling the embodiments of claim 15-19. The 99-Tcm of Lundberg fulfills the specific embodiment of a diagnostic agent and a radioisotope.

Hansen et al teaches that the LL1 antibody is rapidly internalized on cells expressing the MHC I invariant chain (page 295, second column) as measured by a ¹¹¹In chelate of DTPA (page 293, second column, lines 13-14). Hansen et al suggest that the LL1 antibody is useful for the delivery of toxins, drugs or radioisotopes that can kill tumor cells expressing surface Ia, such as B cell lymphomas (page 299, last paragraph).

It would have been prima facie obvious at the time the claimed invention was made to substitute the LL1 antibody for the LL2 antibody in the composition taught by Lundberg et al. One of skill in the art would have been motivated to do so by the teaching of Hansen regarding the ability of LL1 to be rapidly internalized and the suggestions by both Pawlak-Byczkowska et al and Hansen et al that the LL1 antibody is useful for targeting B cell lymphomas and other B cell malignancies that express the invariant chain antigen bound by LL1.

Claims 1-10, 13-21, 27, 35-38 and 125 rejected under 35 U.S.C. 103(a) as being unpatentable over Pawlak-Byczkowska et al, Juweid et al, Lundberg et al and Hansen et al as applied to claims 1-10, 13-21, 27, 35, and 125 above, and further in view of Schlom (In: Molecular Foundations of Oncology, Sameul Broader, Ed, 1991, pages 95-134)..

Schlom teaches that in all of the previous reported human trials in which non-immunosuppressed patients were treated with multiple doses of murine antibodies only the first and perhaps the second dose of said antibody was efficiently reaching the tumor site due to the HAMA response. Schlom teaches that it is unrealistic to assume that just one or two administrations of any anti-cancer therapeutic would be effective. Schlom teaches that the answer to this problem is the humanization of the murine antibodies (pages 97-98, bridging paragraph). Schlom also teaches that F(ab')₂ or Fab' fragments also help reduce the HAMA response (page 119 second column, lines 16-17 under the heading "Single Chain Antigen Binding Proteins). Schlom also teaches that scFv although comparable in binding affinity to Fab' have a more rapid plasma clearance than the Fab' fragment resulting in a greater tumor to

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tissue ratio. Schlom also points out that the small size of the scFv improves the capacity for penetration through the tumor mass.. Schlom also points out that scFv are easier to make than F9ab')² of Fab' fragments.

It would have been prima facie obvious at the time the claimed invention was made to provide a humanized LL1 antibody or a humanized LL1 antibody fragment, such as an scFv. One of skill in the art would have been motivated to do so by the teachings of Schlom on the necessity of avoiding the HAMA response.

Claims 1-10, 13-21, 27, 35-38, 40 and 125 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pawlak-Byczkowska et al, Juweid et al, Lundberg et al, Hansen et al and Schlom as applied to claims 1-10, 13-21, 27, 35-38 and 125 above, and further in view of Greenwood et al, 'Effector functions of attached sets of recombinant human IgG subclass antibodies', In: Protein engineering of antibody molecules, for therapeutic and Prophylactic Applications in Man, Clark, Ed., 1993, pages 89 and 97).

Greenwood et al teach that for some applications it may be necessary to use an antibody isotype which is non depleting and merely targets the antigen (lines 5-6), such as IgG4, or any of the IgG2 or IgG3 which have less ability to activate complement and ADCC.

It would have been prima facie obvious at the time the claimed invention was made to use a human constant region which was IgG2a or Ig3 or Ig4. One of skill in the art would have been motivated to do so in order to have a "non-depleting" antibody which functions to bind and be rapidly internalized with and effector molecule which is a radioisotope, toxin or drug. One of skill in the art would have been motivated to do so by the teachings of Hannsen et al on the rapid internalization of the LL1 antibody and the suggestion by Greenwood et al that some applications require only a antibody targeting function.

Claims 1-10, 13-21, 23, 27, 35, and 125 rejected under 35 U.S.C. 103(a) as being unpatentable over Pawlak-Byczkowska et al, Juweid et al, Lundberg et al and Hansen et al as applied to claims 1-10, 13-21, 27, 35, and 125 above and in further view of Nakagawa et al, (Journal of Neurooncology, 1999, vol. 45, pp. 175-183).

Claim 23 embodies the composition of claim 21 further comprising FUDR-dO Nakagawa et al teach the treatment of a patient with metastatic lymphoma to the brain with 5-fluorodeoxyuridine (Table 1, patient #16).

It would have been prima facie obvious to one of skill in the art to use FUDR-dO within the liposomes taught by Lundberg to target non-cranial B lymphoma cells. One of skill in the art would have been motivated to do so by the suggestion by Lundberg et al that the liposomes are good carriers of drugs and the teachings of Hannsen et al on the internalization of antibodies which bind to the CD74 receptors which are present on lymphoma cells. One of skill in the art would have concluded that the killing of the cranial metastatic lymphoma cells by intrathecal administration was indicative that lymphoma cells targeted by the LL1 antibody would be similarly sensitive to the FUDR-dO. \

Applicant argues that because 09/307,816 used in the above rejection fulfills the specific requirement of a "nanoparticle", the instant priority should be extended to before the filing date of the '816 application. This has been considered and not found persuasive. The description of a specific species of the claimed genus of nanoparticles "submicron emulsion" does not suffice to describe an entire genus of "nanoparticles" as stated above in response to applicant's arguments regarding the priority date. Further, disclosure in an application that merely renders the later-claimed invention obvious is not sufficient to meet the written description requirement of 35 USC 112, first paragraph. [Lockwood v American Airlines, Inc., 41 USPQ.2d 1961 at 1966 (CAFC, 3/4/97)].

Applicant argues that it would not have been obvious to conjugate the LL1 antibody to a lipid emulsion in the same manner as the LL2 antibody was conjugated to a lipid emulsion because Hansen et al teach that the uptake of the CD74 receptor is much more rapid. This has been considered but not found persuasive. Lundberg et al teach that the problem of rapid uptake by mononuclear phagocytes is overcome by grafting polyethylene chains on the particle surfaces with the monoclonal antibody linked to the distal PEG terminus (page 1100, first column, lines 1-9). One of skill in the art would have been motivated to conjugate the LL1 antibody to the same substrate as used for the LL2 antibody in order to overcome non-specific uptake by phagocytes before the antibody reaches the CD74 target. Applicant has provided a "in

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press manuscript". However, the information therein will not be discussed because the obviousness rejection is based on what one of skill in the art would have considered as obvious as of the earliest priority date. MPEP 2143.02 states:

*PREDICTABILITY IS DETERMINED AT THE TIME THE INVENTION
WAS MADE*

Whether an art is predictable or whether the proposed modification or combination of the prior art has a reasonable expectation of success is determined at the time the invention was made. Ex parte Erlich, 3 USPQ2d 1011 (Bd. Pat. App. & Inter. 1986)

The "in press manuscript" does not constitute the state of the art at the time the invention was made.

Applicant argues that Schlom and Greenwood do nothing to cure the deficiencies of the combination of Pawlak-Byczkowska et al, Juweid et al, Lundberg et al and Hansen et al, however this is unpersuasive for the reasons set forth above in defense of Pawlak-Byczkowska et al, Juweid et al, Lundberg et al and Hansen et al.

Claims 1, 5, 8, 11, 12, 19, 20, 30, 35-38 and 125 rejected under 35 U.S.C. 103(a) as being unpatentable over Rybak et al (U.S. 6,395,276).

Rybak et al teaches an immunotoxin comprising the LL1 antibody, wherein said antibody is attached to the toxic moiety by either conjugation or recombinant means (column 12, line 47 to column 1, line 4). Rybak et al specifically teaches the LL1 immunotoxin comprising onconase (figure 3). Rybak et al teach that "Onconase" is an RNase thus fulfilling the specific requirements of an effector which is an enzyme. Rybak et al teach that immunotoxins which are directed to CD74 are useful for the treatment of B-cell malignancies wherein said B-cell has a class II invariant chain, as well as melanoma, neuroblastoma and ,myeloma (column 8, lines 64-67 and column 9, lines 55-60). Rybak et al also teach the LL2 antibody which binds to CD22 and expressed on the surface of malignant B-cells (column 9, lines 43-49). Rybak et al teach that humanized antibodies and single chain antibodies are part of the invention (column 10, lines 36-

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39). Rybak et al suggest possible chemical modifications of the immunotoxins of the invention include derivitization with PEG to extend half-life in the circulatory system and reduce immunogenicity as is well known in the art..

It would have been prima facie obvious at the time the claimed invention was made to derivatize the LL1-immunotoxin and the LL2 immunotoxin of Rybak with PEG by methods well known in the art. One of skill in the art would have been motivated to do so by the suggestion of Rybak et al who stated that it was well known in the art. Further, it would have been obvious to use both derivatized immunotoxins together for the treatment of B cell malignancies. The instant situation is amenable to the type of analysis set forth in *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to produce a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been taught individually in the prior art.

Claims 1, 5, 8, 11, 12, 19, 20, 30, 31, 35-38 and 125 rejected under 35 U.S.C. 103(a) as being unpatentable over Rybeck et al (U.S. 6,395,276) as applied to claims 1, 5, 8, 11, 12, 19, 20, 30, 35-38 and 125 above, and further in view of Bagshawe et al (Curr Opin Immunol, 1999, Vol. 11, pp. 579-583)..

Claim 31 embodies the composition of claim 30 wherein the enzyme is selected from a carboxyesterase, a glucuronidase, a carboxypeptidase a beta-lacatamase, a phosphatase and mixtures thereof.

The teaching of Rybak et al render obvious the enzyme of Onconase. Rybak et al do not specifically suggest the use other enzymatic effectors.

Bagshawe et al teaches enzymatic effectors targeted to cancer cells which include a glucuronidase, a carboxypeptidase a beta-lacatamase, and a phsophatase (page 580, Table 2).

It would have been prima facie obvious at the time the claimed invention was made to use an LL1 immunotoxin conjugated to PEG as suggested by Rybak et al, wherein the immunotoxin was a glucuronidase, a carboxypeptidase a beta-lacatamase, or a phsophatase. One

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of skill in the art would have been motivated to do so by the teachings of Bagshawe et al regarding the use of said enzymes in prior antibody targeted cancer therapies..

Claims 1, 5, 20, 21, 24-29 and 125 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hua et al (Human Pathology, 1998, Vol. 29, pp. 1441-1446) in view of Torchilin et al (Crit Rev Ther Drug Carriers, 1991, Vol. 7, pp. 275-308).

Hua et al teach that the LN2 is a monoclonal antibody to CD74 which is expressed in non-small cell lung carcinoma and dysplastic and neoplastic epithelium such as thyroid, esophagus, colon, lung, breast and stomach (page 1445, Table 3 and second column, first full paragraph). Hua et al do not teach the chelation of LN2 to polymers carrying radionuclide complexes via hard or soft chelators.

Torchilin et al teach the chelation of antibodies to polymers carrying the radiolabels including Bi, ^{99m}Tc and ⁶⁸Ga, (page 290, line 8 and page 277, line 11 from the bottom of the page and page 303, line 6 from the bottom of the page), which fulfills the specific embodiments of claims 25-29. Torchilin et al teach the chelator of DTPA (page 278) which fulfills the specific embodiment of claims 24 and 27. Torchilin et al teach that polymers bearing the radiolabels can be chelated to targeting antibodies and result in improved radioimaging in vivo (pp. 292-303).

It would have been prima facie obvious at the time the claimed invention was made to make a conjugate to LN2 with a radio labeled polymer for the in vivo immunodetection of non-small cell lung cancer and the detection of cancer or precancer of the thyroid, esophagus, colon, lung, breast and stomach. One of skill in the art would have been motivated to do so by the teachings of Torchilin et al on the improvements afforded to antibodies by the conjugation to polymers bearing detectable labels.

Claims 1, 5, 34 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hua et al (Human Pathology, 1998, Vol. 29, pp. 1441-1446) in view of O'Reilly et al (U.S. 5,792,845) and Kratz et al (Crit Rev Drug Carrier Sys, 1999, Vol. 16, pp. 245-288).

Hua et al teach that the LN2 is a monoclonal antibody to CD74 which is expressed in non-small cell lung carcinoma and dysplastic and neoplastic epithelium such as thyroid, esophagus, colon, lung, breast and stomach (page 1445, Table 3 and second column, first full

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paragraph). Hua et al do not teach the chelation of LN2 to polymers carrying the antiangiogenic agent of angiostatin.

O'Reilly et al teach that angiostatin inhibits the growth of breast cancer and lung cancer (claim 16).

Kratz et al teach the delivery of drugs via drug-polymer conjugate comprising an acid sensitive linkage which is released in vivo at the tumor site (abstract). Kratz et al also teach immunotoxins conjugated to polymers (pp. 272-276).

It would have been prima facie obvious at the time the invention was made to make a drug polymer conjugate comprising the LN2 antibody of Hua with the angiostatin of O'Reilly et al. One of skill in the art would have been motivated to do by the teachings of Hua et al identifying breast cancer and lung cancer as over expressing the LN2 antigen, and the teachings of O'Reilly et al identifying breast cancer and lung cancer as benefiting from the antiangiogenic effect of angiostatin. One of skill in the art would have understood from the teachings of Kratz et al that the angiostatin would be released in the vicinity of the tumor due to an increased pH in said vicinity and therefore by providing an antiCD74 targeted polymer comprising angiostatin linked by a acid sensitive linkage a higher concentration of free angiostatin would be realized at the tumor site relative to the general circulation.

All claims are rejected.

All other rejections and objections as set forth or maintained in the prior Office action are withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Karen A. Canella/

Ph.D., Primary Examiner

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